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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
JOYCE, CATHERINE	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/670,472	MA ET AL.	
	Examiner	Art Unit	
	Catherine M. Joyce	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,11 and 27-46* is/are pending in the application.

4a) Of the above claim(s) *46* is/are withdrawn from consideration.

5)☒ Claim(s) *1,11, 27-31, and 33* is/are allowed.

6)☒ Claim(s) *32 and 34-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 9, 2007 is acknowledged and has been entered. An action on the RCE follows.

2. Claims 2-10 and 12-26 are canceled, claims 1, 11, and 27-46 are pending, claim 46 is withdrawn from consideration as being drawn to a non-elected invention, and claims 1, 11, and 27-45 are under examination.

3. The following rejections are being maintained:

4. Claims 45 remains rejected under 35 USC 112, first paragraph, for the reasons set forth previously in the Paper mailed April 25, 2006, Section 6, pages 8-9 and the Paper mailed November 16, 2006, Section 4, pages 2-3.

Applicant argues that the claim is enabled because all that is required is that the peptide bind and because the Office Action, allegedly, did not set forth any arguments to show that the peptide of SEQ ID NO:5 would not function in a similar manner as the peptide of SEQ ID NO:3.

Applicant's arguments have been considered but have not been found to be persuasive. The specification teaches that the identity of the last amino acid of the exemplified peptide of SEQ ID NO:3 can significantly affect the predicted HLA binding affinity of the peptide and George et al. (2005, Trends in Immunology 26(12):653-659), as set forth previously, teach that the specificity of the interaction with which a T-cell receptor recognizes antigen in the form of a peptide held in the groove of an MHC class molecule is such that a single amino acid substitution in the peptide can abolish the ability of T cells to respond to the antigen or can convert the peptide to an antagonist peptide that "turns off" the ability of a population of T cells to respond by proliferation.

Given that the claims are drawn to peptides having terminal amino acids that differ in size, shape, and charge from the exemplified valine, given that the prior art teaches that a single amino acid change in a peptide can be critical in terms of T cell recognition, and given that the specification teaches that the terminal amino acid is predicated to effect HLA binding, one of skill in the art could not predict that peptides having the sequence ALKDVEERA (SEQ ID NO:5) will be useful in accordance with the invention. Thus, practice of the invention would require undue experimentation.

New Grounds of Rejection

Claim Rejections - 35 USC 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 34-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to

make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations.". (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to the following:

A method for inducing an immune response in a subject in need thereof comprising administering a composition comprising an effective amount of a peptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NO: and an adjuvant, wherein said effective amount is sufficient to induce an immune response in said subject (**claim 34**);

wherein said immune response is a stimulation of cytolytic T cells specific for complexes of an HLA and said peptide (**claim 35**);

wherein said subject has cancer and wherein the subject's cancer cells express MAGE-C2 (**claim 36**);

wherein said cancer cells expresses HLA-A2 (**claim 37**);

wherein said composition comprises a non-tumorigenic cell presenting a complex of the peptide and an HLA-A2 molecule (**claim 38**);

wherein said non-tumorigenic cells are transfected with a nucleic acid molecule that encodes the peptide (**claim 39**);

wherein said non-tumorigenic cells are transfected with a nucleic acid molecule that encodes the peptide and a nucleic acid molecule which encodes the HLA-A2 molecule (**claim 40**);

wherein said non-tumorigenic cells are transfected with a nucleic acid molecule that encodes both the peptide and the HLA-A2 molecule (**claim 41**);

wherein said composition comprise s a complex of the peptide and an HLA-A2 (**claim 42**);

and

A method for treating a subject with a disorder characterized by the presence of complexes of an HLA-A2 molecule, and a peptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 3 presented on surfaces of cells associated with said disorder, comprising administering to said subject an amount of cytolytic T cells, which are specific for complexes of said HLA-A2 molecule and said peptide, wherein said amount is sufficient to alleviate said disorder (**claim 43**);

And

A method for inducing a response by cytolytic T cells (CTLs) in a subject having a disorder characterized by the presence of complexes of an HLA-A2 molecule and a peptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 3 presented on surfaces of cells associated with said disorder, wherein said CTLs are specific for said complexes by administering to said subject an agent which induces a response by said CTLs wherein said response is proliferation, release of TNF alpha or lysis of cells presenting said complex (**claim 44**).

The specification teaches that a cytotoxic T lymphocyte (CTL) was identified by establishing a melanoma tumor cell line, EB81-MEL.2, from a patient EB81, coculturing the tumor cell line with lymphocytes from the patient, and identifying the CTL clone 606 C/22.2 which lyses the EB81-MEL.2 cell line, by limiting dilution (page 40, lines 8-20).

The specification teaches that patient EB81 had been vaccinated with DNA vaccine encoding a MAGE-1 peptide and a MAGE-3 peptide, and with the peptides, wherein the peptides are unrelated to the MAGE-C2 peptide described below (page 42, lines 4-9), and that the CTL clone did not recognize cells pulsed with the peptides used for vaccination (page 40, lines 13-20). The specification also teaches that the gene encoding the antigen was identified as MAGE-C2 by preparing a plasmid cDNA library from mRNA isolated from the EB81 melanoma patient, transfecting cells with the library to form a library of transfected cells, adding the CTL clone to the transfected cells, and identifying reactivity via measurement of TNF production (page 40, lines 21-29). The specification teaches that the newly isolated MAGE-C2 cDNA differed from previously described MAGE-C2 cDNAs by the presence of short intronic sequence that is not splice out that is located in the 5'-untranslated region of the gene and does not affect the coding region (page 41, lines 1-7). The specification teaches that the reactive portion of the MAGE-C2 antigen was identified by constructing minigenes of MAGE-C2 cDNA, transfecting cells with the minigenes, and identifying reactivity via TNF production, wherein it was determined that the peptide was encoded with the last 211 nucleotides of the open reading frame of the MAGE-C2 DNA (page 41, lines 14-18). The specification teaches that several candidate peptides bearing the binding motif for HLA-A2 were synthesized, and the nona-peptide ALKDVEERV (SEQ ID NO:3) was found to stimulate TNF release by cells of the CTL clone (page 41, lines 14-18). The specification further teaches that recognition of the peptide of SEQ ID NO:3 was confirmed by a lysis assay of autologous EBV transformed EB81 lymphocytes cells pulsed with the peptide (page 41, lines 14-24). The specification also teaches that the frequency of CTL 606C/22.2 cells to CD8 cells was determined in samples of PBMCs and in melanoma tumor samples from patient EB81, with frequencies of cells of $4x10^{-5}$ and 10^{-1} thru 10^{-2}, respectively, thus indicating an enrichment of the CTL cells in the tumor sample versus the PBMCs (page 43, lines 10-33). The specification also teaches that a series of allogeneic HLA-A2 tumor lines were tested and several were recognized by the identified CTL clone, as determined using a TNFα production assay, including AVL3-MEL, LB373-MEL, and myeloma U266 (page 40, lines 16-19). The specification

references Lucas et al. (2000, Int. J. Cancer 87:55-60), Gure et al. (2000, Int. J. Cancer 85:726-732), and U.S. Patent No. 6,475,783 as teaching that MAGE-C2 is expressed in about 40% of melanomas (page 40, lines 27 thru page 41, line 1). The specification also teaches that the "status of a tumor" may be monitored by comparing the magnitude of the response by CTLs in a test sample as compared to a control (page 15, lines 3-12).

The teaching of the specification cannot be extrapolated to enable the scope of the claims because the teaching in the specification that the isolation of reactive T cells in a melanoma patient that recognize the peptide of SEQ ID NO:3 presented in an HLA-A2 context is not sufficient to predictably establish that the peptide of SEQ ID NO:3 could be used for the treatment of any disease including cancer.

In particular, it is well known in the art that cancer treatment is unpredictable, and that a problem with tumor tolerance and the loss of surface Class I MHC is well known. For example, Smith RT, 1994, Clin Immunol, 41(4): 841-849, teaches that antigen overload, due to antigen shedding by actively growing tumor, could block specifically either cytotoxic or proliferative responses of tumor specific T cells (p. 847, last paragraph bridging p.848 and p.848). Smith further teaches that many tumors progressively lose MHC representation at the surface of the cell, and the loss of surface Class I MHC could severely limit the possibility for cytotoxic T cells specific for a tumor specific antigen to find said tumor specific antigen in the necessary MHC context (p.484).

Similarly, Boon (Adv Can Res, 1992, 58:177-210) teaches that for active immunization in human patients, the stimulation of immune defenses of organisms that have often carried a large tumor burden is required. Thus, establishment of immune tolerance may therefore have occurred and it may prevent immunization, and several lines of evidence suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, para 2). In addition, Boon teaches that even if activated CTLs are significantly increased, the therapeutic success remains

unpredictable due to inconsistencies in antigen expression or presentation by tumor cells (p.178, paragraph before last paragraph). Further, Kirkin et al, (1998, APMIS 106:665-679) et al. teach that in particular for tumor antigens, due to the existence of self-tolerance, only T cells with low affinity T-cell receptors are produced (abstract) and Chaux et al. (1998, Int. Int J Cancer 77: 538-542) teach that some of the CTLs have an affinity that is too low for the recognition of cells that have processed the antigen, which situation is different from the *in vitro* conditions disclosed in the specification wherein the synthetic peptides are in high number when incubated with the cells (p.541, second column, second paragraph). In particular, Kirkin et al, *supra*, review several tumor-associated antigens and conclude that initiation of a strong immune response in vivo is an extremely rare event (p.674, first column, last paragraph). Kirkin et al. teach that although several peptides of tumor associated antigens have been identified as recognized by CTL in vitro, and peptides from MAGE-A1 and MAGE-A3 have been tested for their ability to induce anti-TUMOR immune response in vivo, only one of the peptides, peptide EVDPIGHLY of MAGE-A3, has limited anti-tumor activity, indicating their low immunogenicity (p.666, second column, second paragraph, last 6 lines). Further, even this peptide EVDPIGHLY of MAGE-A3 produces a very low level of CTL response which is detectable only by a very sensitive method, as taught by Chaux et al, Int J Cancer, 1998, 77: 538-542 (abstract). Given the above, even if a peptide was recognized by T-cells *in vitro*, it could not be predicted that the T-cells would recognize these peptides *in vivo*.

Further, White et al. (Ann. Rev. Med., 2001, 52:125-145), although drawn to antibody recognition on the cancer cell surface, would equally apply to CTL recognition of a specific epitope on the cancer cell surface. White teaches that, for a successful immunotherapy, besides specificity of the antigen, other properties of the antigen should be considered including that (1) that the antigen should be present on all or near all of the malignant cells to allow effective targeting and to prevent a subpopulation of antigen-negative cells from proliferating and (2) whether the antigens shed, modulate or internalize influence that effectiveness of the administered immunotherapy (i.e. the antibody) (p. 126, second paragraph). Additionally, antigen internalization or downregulation can cause repeat dosing to be unsuccessful due to the disappearance of the antibody target (p. 126, paragraph before last).

Further, the goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, Ezzell (J. NIH Res, 1995, 7:46-49) reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph) and further states that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (p 48, para 6). In addition, Spitler (Cancer Biotherapy, 1995, 10:1-3) recognizes the lack of predictability in the art when she states that "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response." (p 1, para 1).

Further, there is insufficient guidance in the specification regarding the parameters which correlate with the ability to stimulate and generate specific CTLs with high affinity that recognize the peptide of SEQ ID NO:3 on the in vivo malignant cell

surface and kill the malignant cells. The specification does not provide any guidance, such as by way of working examples, on the degree of expression of the peptide of SEQ ID NO:3 on the surface of malignant cells that would result in the lysing of the malignant cells by T-cells specific for the peptide of SEQ ID NO:. In fact, the specification does not provide any data on the expression of the peptide on the surface of primary tumor cells.

In view of the above, one cannot predict whether the CTL target antigen is expressed in sufficient amount on the surface of target tumor cells or whether effective CTLs could be generated by the peptide in vivo, or whether therapeutic CTLs would be effective. Thus it would require undue experimentation to practice the claimed methods.

7. Claim 32 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim is drawn to the following:

A method for monitoring status of a tumor, comprising contacting a sample taken from a patient having a tumor with an isolated complex comprising a first and second binding partner which are specific for each other, wherein said second binding partner is bound to a plurality of tetramers of an HLA-A2 molecule, a g2 microglobulin molecule, and the peptide of consisting of amino acid sequence ALKDVEERV (SEQ ID NO:3),

assaying the sample for a level of cytolytic T cell response, and

comparing the response level of the cytolytic T cells in the sample to a known

level of cytolytic T cell response to monitor the status of said tumor (**claim 32**).

It is noted that the term "status of a tumor" is not defined by the claims or the specification and thus, for examination purposes, this term is interpreted to mean any

status of the tumor such as the metastasis of the tumor, the potential of the tumor to metastasize, etc.

The specification teaches as set forth above. The specification also contemplates that the "status of a tumor" may be monitored by comparing the magnitude of the response by CTLs in a test sample as compared to a control (page 15, lines 3-12).

The teaching of the specification cannot be extrapolated to enable the claim because one of skill in the art could not predict that the level of CTL response in the sample could be correlated with a particular tumor status other than the presence of a tumor. In particular, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to the use of CTL levels for monitoring tumor status. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence of the marker and confirm marker predictive value in prospective population trials (see abstract). Pertinent to the instant rejection, there is no evidence presented in the specification or the art of record that CTL response for CTLs that recognize the peptide of SEQ ID NO:3 can be correlated with any status of the tumor other than the presence of the tumor. Tockman goes on to teach that markers have clear biological plausibility **if validated** (p. 2713s, col 1). The specification provides insufficient guidance with regard to this issue such as, for example, by way of working examples that demonstrate that any particular status of a tumor can be assessed by determining CTL levels. Thus, in view of the teaching in the art on the necessity to validate cancer markers and on the absence of guidance in the specification as to what particular status of cancer can be correlated with different leves of CTL reactivity, it appears that undue experimentation would be required to practice the claimed invention.

8. Claims 1, 11, 27-31 and 33 are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine M. Joyce whose telephone number is 571-272-3321. The examiner can normally be reached on Monday thru Friday, 10:15 - 6:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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